REMARKS AND ARGUMENTS

Claims 33-61 have been examined, and claim 61 is indicated as allowable. Claims 33-60 are rejected.

Claim Amendments. Claims 35. 37-39, 47, and 49-51 are amended to address the 35 U.S.C. § 112 rejection in paragraph numbered 4 of the Office Action (page 7). It is believed that the amendments to the claims overcome the rejection interposed.

Claims Rejections. Claims 33-60 are rejected solely on the basis of 35 U.S.C. § 112, second paragraph. This rejection is respectfully traversed for the reasons set forth below.

At the heart of this invention is the discovery that thrombopoietin can be employed to increase endogenous platelet-derived growth factors by increasing platelet concentrations, which in turn thereby effect myelin repair or regeneration. Thrombopoietin was developed and clinically tested to treat thrombocytopenia, generally secondary to chemotherapy. See, e.g., Saroj Vadhan-Raj: Recombinant human thrombopoietin: clinical experience and in vivo biology. *Seminars in Hematology*, 35:261-268 (1998). (All citations to prior art are to articles cited in an Information Disclosure Statement of record.) In thrombocytopenia, the objective is to increase depressed platelet levels to a higher level, ideally to a level approximating normal. However, as the Vadhan-Raj article makes clear (page 261, second column) it is known that administration of thrombopoietin results "in an increase in platelet counts by several-fold in normal animals..." Thus it was known that thrombopoietin administered to normal subjects results in an increase in platelet counts. However, until the instant invention no medical condition was described for which increasing platelet counts above normal ranges was desirable.

The invention thus describes a method of using a known drug, thrombopoietin, to increase platelet counts, thereby necessarily increasing the endogenous product of platelet-derived growth factors. This is done specifically to treat neurological disorders, such as by inducing myelin repair or regeneration.

It was known that platelet-derived growth factors could be used to induce myelin repair or generation. See, e.g., C. Fressinaud et al: Platelet-derived growth factor partly prevents chemically induced oligodendrocyte death and improves myelin-like membranes repair in vitro. *GLIA*, 16:40-50

(1996); J. B. Grinspan et al: Protein growth factors as potential therapies for central nervous system demyelinative disorders. *Annals of Neurology*, 36:S140-S142 (1994); F. A. McMorris and R. D McKinnon: Regulation of oligodendrocyte development and CNS myelination by growth factors: prospects for therapy of demyelinating disease. *Brain Pathology* 6:313-329 (1996).

It was also known that various "regulatory agents", such as thyroid hormone and thyrotropin, may be employed to effect direct or indirect alteration of cell division rates and induction of differentiation, specifically of oligodendrocyte cells. The effect of these regulatory agents are described generally in Rodriguez-Pena A: Oligodendrocyte development and thyroid hormone. *J. Neurobiol* 1999, Sep. 15;40(4):497-512; Ahlgren SC, Wallace H, Bishop J, Neophytou C, Raff MC: Effects of thyroid hormone on embryonic oligodendrocyte precursor cell development in vivo and in vitro. *Mol Cell Neurosci* 1997;9(5/6);420-32; Gao FB, Apperly J, Raff M: Cell-intrinsic timers and thyroid hormone regulate the probability of cell-cycle withdrawal and differentiation of oligodendrocyte precursor cells. *Dev Biol* 1998 May 1;197(1):54-66; Ahlgren SC, Wallace H, Bishop J, Neophytou C, Raff MC: Effects of thyroid hormone on embryonic oligodendrocyte precursor cell development in vivo and in vitro. *Mol Cell Neurosci* 1997;9(5/6);420-32; and Durand B, Raff M: A cell-intrinsic timer that operates during oligodendrocyte development. *Bioessays* 2000 Jan; 22(1):64-71.

It is against this specific knowledge in the art that enablement must be measured. (See MPEP § 2164.05, requiring consideration of evidence as to the state of the art.) The state of the art at the time of filing demonstrates that platelet-derived growth factors induce myelin repair. The state of the art further demonstrates that various regulatory agents may be employed to effect cell division rates and induction of differentiation with oligodendrocyte cells. In the invention thrombopoietin is used to increase platelet production, thereby effecting an increase in endogenous platelet derived growth factors, either without a thyroid regulator agent (claims 57-60), or with a thyroid regulatory agent (claims 45, 46, 51-56).

The arguments advanced in the Office Action do not demonstrate either the requisite factual predicate for an enablement rejection (See MPEP § 2164.04), or demonstrate that "undue experimentation" would be required. As stated in *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370

(CCPA 1971), "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

There are, for example, no references cited in the Office Action suggesting that either there is any uncertainty as to the effect of thrombopoietin to increase platelet levels, or suggesting any uncertainty that such increases would result in increased platelet-derived growth factors. Thus it is a matter of simple and routine experimentation to determine optimal quantities, frequency of administration and the like. As the declaration of Dr. Schwartz states (previously filed), the "conduct of clinical trials ... is well known in the art, and is a routine and customary part of the development of any drug for use with humans." There is no factual assertion establishing a lack of enablement. No references are supplied relevant to a lack of enablement (MPEP § 2164.04 provides "[r]eferences should be supplied if possible to support a *prima facie* case of lack of enablement"). There are no "specific technical reasons" advanced to demonstrate lack of enablement. MPEP § 2164.04.

It is respectfully submitted that the scope of claims is comparatively narrow, related to use of thrombopoietin either with or without a thyroid regulatory agent, to induce an increase in platelet levels, thereby resulting in a necessary increase in platelet-derived growth factor production with attendant beneficial effects for treatment of neurological disorders involving damage to myelin. With respect to thyroid regulatory agents, which are employed in the invention only as an adjunct to thrombopoietin and only in some, but not all, claims, the scientific literature and teaching of the patent is sufficient.

The concluding paragraphs of the rejection address only "unpredictability" regarding thyroid regulatory agents (see, e.g., page 6 of the Office Action). It is submitted that the disclosure is enabling for thrombopoietin alone, and no factual argument is raised in the Office Action as to this embodiment (e.g., claim 57).

Formal Matters. Authorization is given to charge payment of any additional fees required, or credit any overpayment, to Deposit Account 13-4213. A duplicate of this paper is enclosed for accounting purposes. Filed herewith is a Petition for Extension of Time to May 30, 2003, with the appropriate fee.

Should the Examiner have any queries, suggestions or comments relating to a speedy disposition of the application, the Examiner is invited to call the undersigned. Allowance of the claims is respectfully requested.

Respectfully submitted,

PEACOCK, MYERS & ADAMS, P.C.

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By: _____

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